stimulants are relatively contraindicated in bipolar disorder, they may be helpful for DMDD. Data support the use of atypical antipsychotic medication in youth with autism and irritability, and in youth with aggression[2]. However, recent increases in antipsychotic prescriptions may have resulted in part from attempts to treat pediatric irritability, perhaps without adequate exploration of alternative pharmacologic and psychotherapeutic approaches[10]. Selective serotonin reuptake inhibitors (SSRIs) may treat irritability in adults; such an approach in children is supported by the high comorbidity and longitudinal associations among irritability, anxiety and depression[2]. SSRIs are now being tested in youth with DMDD.

Psychotherapeutic approaches are likely to be important in the treatment of irritability. Parent training can decrease a child's aggression and might also decrease irritability[11]. Cognitive behavioral approaches are being tested, as is implicit training designed to alter irritable children's tendency to view ambiguous faces as angry[8].

In conclusion, the recent focus on irritability has yielded considerable knowledge about its longitudinal course and associations with psychopathology. Ongoing work is aimed at identifying the brain mechanisms mediating irritability and at using that knowledge to inform novel treatment approaches.

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Are there new advances in the pharmacotherapy of autism spectrum disorders?

Autism spectrum disorders (ASD) are heterogeneous neurodevelopmental disorders beginning early in childhood and characterized by social communication deficits and restricted patterns of repetitive/stereotypic behaviors. Associated symptoms such as hyperactivity, irritability, insomnia, seizures, gastrointestinal and immunological disturbances may be present. Some ASD children have exceptional (savant) abilities in isolated cognitive areas such as mathematical, artistic or musical skills. ASD are more common in boys than girls (ratio 4:1), but are under-diagnosed in the latter.

The etiology of ASD is quite complex. Genetic, epigenetic, infectious, autoimmune-immunologic, metabolic, nutritional and toxic factors may be involved. Different brain areas, neural circuits, neurotransmitters, neuropeptides, cytokines, synaptic and signal transduction molecules and processes may be affected.

Because of this complexity, the development of pharmacotherapy for ASD has proven quite challenging. The marked heterogeneity of these disorders suggests that different treatments will likely be beneficial for different patients. There is a need for early detection and intervention when the brain is more plastic and changes may be more easily reversible; however, some studies suggest that pharmacotherapy may also be useful in adults. Biomarkers may help stratify subgroups and predict response to therapy. The ultimate goal is to target the ASD core symptoms; however, most current pharmacotherapies target ASD-associated symptoms.

The atypical antipsychotics risperidone and aripiprazole are approved in the US for the treatment of disruptive behaviors (aggression, self-injury, temper tantrums) in childhood ASD. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and citalopram, have been studied in ASD: single-site trials demonstrated efficacy for repetitive behaviors in ASD children and adults[1,2], but multi-site trials failed to document efficacy, except in a subgroup of subjects with high irritability. Anticonvulsants have been studied for disruptive behaviors such as impulsivity, self-injury and aggression, common in ASD: valproate, acting by potentiating the inhibitory effect of the GABAergic system and by epigenetic effects, has shown benefit in reducing irritability and impulsive-aggressive behavior in ASD children[3]. Medications approved for attention-deficit/hyperactivity disorder (ADHD) have been studied in ASD: they have modest efficacy on symptoms such as hyperactivity (methylphenidate, dextroamphetamine, atomoxetine) and irritability (clonidine).

Newer ASD experimental pharmacotherapies target core ASD symptoms and are developed on the basis of knowledge of the molecular neurobiology and genetics of ASD.

One group of such drugs aims to restore the balance of excitation and inhibition in brain cortical regions. They include those targeting metabotropic glutamate receptors (such as mGlu5 antagonists), NMDA receptors (such as the NMDA receptor antagonist memantine), or AMPA receptors (such as

AMPA receptor potentiating drugs, ampakines)[4]. mGlu5 antagonists have been tested in ASD associated with fragile X syndrome, and showed promise in a subgroup of patients[5]. GABAergic agents, such as the GABA-B receptor agonist arbaclofen (STX209), have shown some effect on irritability and social withdrawal in ASD children[6].

The peptide hormone oxytocin is important in social cognition and behavior. In ASD adults, acute intravenous administration of oxytocin reduced repetitive behaviors[7] and improved accuracy of recognizing emotions in speech over time[8]. Intranasal administration improved social cognition in children, adolescents and adults with ASD[9]. A vasopressin 1a receptor antagonist had some effect on speech recognition of emotions such as fear and lust in high-functioning ASD adults.

Insulin-like growth factor 1 (IGF-1) is important in central nervous system maturation, development and connectivity, that are perturbed in ASD. Studies in Shank-3 deficient mice that model Phelan-McDermid syndrome (PMS), which may be associated with some cases of ASD, indicated that IGF-1 may reverse structural changes in ionotropic glutamate receptors, functional synaptic plasticity changes, and excitation/inhibition imbalance. A clinical trial with recombinant human IGF-1 in PMS children showed improvement in social impairment and restricted behaviors[10].

Agents modulating the immune system have been tested in ASD. The immune response induced by the whipworm Trichuris suis ova has shown benefit on the repetitive behavior domain in adult ASD. Immunosuppressive and protein synthesis inhibiting drugs such as the mTOR inhibitor rapamycin have been shown to improve social deficits in some forms of ASD.

The alpha-7 nicotinic acetylcholine receptor (nACR) gene is associated with autism and ADHD. nACR drugs tested in clinical trials include mecamylamine, transdermally administered nicotine, and donepezil. Some alpha-7 nACR antagonists such as galantamine have shown promise in animal models and clinical trials.

Drugs modulating the cannabinoid system, such as cannabidiol, have been found effective in childhood epilepsy, and may be worth studying in ASD due to their anti-anxiety, anti-epileptic, immunomodulating and cognitive-enhancing effects and good safety. Interestingly, social reward and oxytocin induce release of endocannabinoids in nucleus accumbens. In ASD animal models, cannabidiol has some impact on social deficits, repetitive behaviors and irritability.

Complementary and alternative medicine (CAM) treatments have been tested in ASD. However, they are not strictly regulated and have not been studied in large-scale clinical trials. Therefore, their safety and efficacy is not well determined. CAM treatments may complement rather than replace proven therapies for ASD. Melatonin may be used for sleep disorders, omega-3 fatty acids for reducing repetitive behaviors and improving sociability. Vitamin B12 supplements are believed to protect against the oxidative damage in ASD. Curcumin, an active ingredient of turmeric, may be beneficial in ASD, perhaps owing to its anti-oxidant and anti-inflammatory properties. Probiotics such as yogurt may have effects on the gut microbiome and on pro-inflammatory cytokines that may play a role in the pathogenesis of ASD.

In summary, the enormous heterogeneity in ASD complicates development of new pharmacotherapies. Personalized treatments are desirable, and studies of syndromal orphan populations may accelerate drug development. Design of future clinical trials needs to address patient stratification on the basis of biomarkers or etiology (for example, immune-inflammatory) and target populations stratified by clinical symptoms.

New pharmacotherapies such as oxytocin/vasopressin antagonists, anti-inflammatory agents, IGF-1, drugs regulating excitation/inhibition balance, protein synthesis inhibitors, and microbiome-targeting drugs may be of particular promise. Existing drugs such as anticonvulsants, SSRIs and atypical antipsychotics may be beneficial in some patients. It is important to test the effectiveness of drugs in younger children who may benefit most from early intervention. The ultimate goal of ASD pharmacotherapy will be to match the treatment to the underlying molecular mechanisms in individual patients.

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Nonmedical use of prescription drugs in adolescents and young adults: not just a Western phenomenon

Nonmedical prescription drug use, generally defined as use without a prescription or use for reasons other than what the medication is intended for, is a global concern, primarily driven by the high and rising phenomenon of nonmedical use of prescription opioids in young populations. Prescription drugs are legal and hence tend to be more easily available than most illegal drugs.